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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/519,162	08/15/2005	Kazuo Umezawa	09707.0001	4831

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EXAMINER	
PURDY, KYLE A	

ART UNIT	PAPER NUMBER
1611	

MAIL DATE	DELIVERY MODE
08/29/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/519,162	UMEZAWA ET AL.	
	Examiner	Art Unit	
	Kyle Purdy	1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) *13-19 and 21-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8 sheets (10/21/2005, 03/01/2006, 06/01/2006 and 03/13/2008)*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

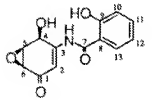
DETAILED ACTION

Election Acknowledged

1. Applicants' election without traverse the invention of Group I encompassing claims 1-12 and 20 is acknowledged. The restriction is made final without traverse.

Status of Application

2. Claims 1-23 are pending, claims 13-19 and 21-23 are withdrawn and claims 1-12 and 20 are presented for examination on the merits.

3. Note, Applicants have elected the following species for examination on the merits:  . The following rejections are made.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. **Claim 4 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.**

6. Claim 4 recites, 'improving at least one symptom resulting from the tumor cell by inhibiting activation of NF-kB'. However, claim 4 depends from claim 3 which recites 'improving at least one symptom resulting from the tumor cell without the contribution of

apoptosis of the tumor cell'. These two claims are inconsistent. Administering DHMEQ (the elected species) would necessarily inhibit of the activation of NF-kB, which in turn would result in enhancing the apoptotic potential of a tumor cell. See Baldwin et al. (J. Clincial Investigation). Baldwin specifically recites, 'Inhibition of NF-kB…..strongly enhances the apoptotic potential'. Thus, the art specially suggests that inhibition of NF-kB would directly affect apoptosis of that particular cell. Therefore, Applicants contrasting claims are unclear and so clarification is requested.

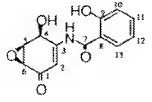
Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. **Claims 1-8, 10, 12 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Matsumoto et al. (Bio. and Med. Chem. Letters 10, 2000, 865-869; of record, see IDS) in view of Takeuchi et al. (US6566394; of record, see IDS), evidenced by Baldwin (J. Clinical Investigation, 2001, 107(3), 241-246) and Morishita et al. (US 6262033).**

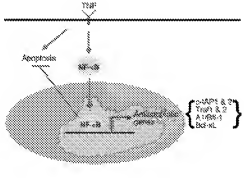
9. Matsumoto is directed to the synthesis of NF-kB activation inhibitors derived from epoxyquinomicin C. Matsumoto specifically teaches the elected species (DHMEQ):



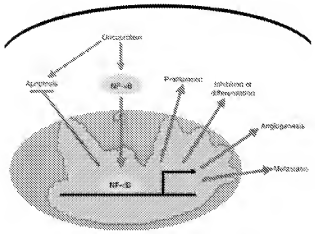
(see page 865).

10. It is taught the DHM2EQ inhibited TNF-a-induced activation of NF-kB in human T cell leukemia cells (see abstract and Figure 3; see instant claims 1, 3, 4, 7, 8, 10 and 20). It is noted that NF-kB is a transcription factor that has been connected with multiple aspects of oncogenesis including the control of apoptosis, the cell cycle, differentiation and cell migration.

11. Baldwin is relied upon to show the basic functions of NF-kB. Baldwin discloses that activation of NF-kB in cancer cells can blunt the ability of cancer therapy to induce cell death (see page 241). In general, NF-kB acts in the following way:



(see page 242) and

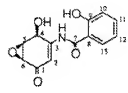


(see page 243). From these illustrations it is quite clear that NF-kB activation induces proliferation, inhibition of differentiation, angiogenesis and metastasis as well as blunts the ability to undergo apoptosis. It is noted that NF-kB activation induces the expression of cell adhesion molecules such as ICAM-1 and angiogenesis inducing molecules such as COX-2 (see page 243; see instant claims 5 and 12). Additionally, Baldwin teaches that inhibition of NF-kB strongly enhances the apoptotic potential of chemotherapy (see page 245; see instant claim 2).

12. Morshita is also relied upon to demonstrate the basic functions of NF-kB. Morshita teaches that by antagonizing the NF-kB DNA promoter sequence results in effectively treating diseases caused by the transcriptional activation of NF-kB. Exemplified diseases include cancer metastasis (see abstract). It is taught that NF-kB (when active) promotes the synthesis of various adhesion factors such as ICAM-1 and VCAM-1 (see column 1, lines 30-35). VCAM-1 is a known endothelial adhesion factor and is known to promote metastasis of cancerous cells (see instant claim 6).

13. Matsumoto fails to specifically teach DHMEQ as being administered to a patient.

14. Takeuchi cures this deficiency. Takeuchi is directed to using NF-kB inhibitors (the instant compound) for the treatment of inflammation with little side effects. It is taught to be suitable for administration to humans through a variety of means (i.e. tablet, injection, etc.) (see column 13-column 14; see instant claim 1).

15. Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Matsumoto and Takeuchi with a reasonable expectation for success in arriving at a method of improving at least one symptom resulting from a tumor cell in a patient in need thereof comprising administering the patient the following compound 

. Matsumoto indicates that DHMEQ is useful for preventing the activation of NF-kB in human T cell leukemia cells. Matsumoto fails to specifically disclose using their compounds on patients with tumors. However, the teaching of Takeuchi cures this deficiency because it discloses using the same compounds for use on human patients for the treatment of inflammation. Albeit true that Takeuchi does not teach administering the compounds to patients with tumors, it would have been obvious to an ordinarily skilled artesian because the prior art indicates the instantly claimed compounds as possessing utility against cancerous cells. Thus, one would have been motivated to use the compounds in hopes of arriving with an effective means for treating cancer in cancer patients. With respect to the limitations that the method inhibit symptoms of cancer such as by improving the chances of apoptosis or by lessening the chances of metastasis, these are obvious. See Baldwin and Morshita. These references are cited to illustrate that such improvement of symptoms in cancer patients would necessarily occur by administering a compound that inhibits

NF-kB activation (e.g. DHMEQ). Baldwin discloses that inhibition of NF-kB would directly affect metastasis by inhibiting the expression of adhesion molecules such as ICAM-1. It is also discussed by Baldwin that COX-2 is transcriptionally activated by NF-kB which results in inflammation and angiogenesis of the cancer cell. Morshita is relied upon to also show NF-kB activation induces the expression of VCAM-1, a well known endothelial cell adhesion factor that also promotes metastasis of cancerous cells. Overall, it is clear that inhibition of NF-kB activation would improve the chances of apoptosis, reduce the chance of metastasis and inhibit intratumoral angiogenesis. It appears that Applicants is describing direct properties of NF-kB activation and inactivation. Therefore, a method of administering DHMEQ to a patient with a tumor to improve their symptoms is *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in absence of evidence to the contrary.

16. **Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over Matsumoto et al. (Bio. and Med. Chem. Letters 10, 2000, 865-869; of record, see IDS) in view of Takeuchi et al. (US6566394; of record, see IDS) and Baldwin (J. Clinical Investigation, 2001, 107(3), 241-246), evidenced by Baldwin (J. Clinical Investigation, 2001, 107(3), 241-246) and Morishita et al. (US 6262033).**

17. Matsumoto and Takeuchi are relied upon for disclosure described in the rejection of claims 1 and 3 under 35 U.S.C. 103(a).

18. Matsumoto and Takeuchi fail to teach the tumor being a breast cancer cell.

19. Baldwin cures this deficiency. Baldwin states that NF-kB is disregulated in breast cancer cells and that NF-kB is typically localized in the nucleus (activate), rather than in the cytoplasm (inactive) (see page 242; see instant claim 9).

20. Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Matsumoto and Takeuchi with a reasonable expectation for success in arriving at a method of treating breast cancer cells with DHMEQ. Matsumoto and Takeuchi are discussed above. Briefly, Matsumoto and Takeuchi motivate a method of administering DHMEQ to a patient with a tumor to reduce the symptoms of that tumor. They however fail to teach administering the compound to a subject with breast cancer. Baldwin cures this deficiency. Baldwin teaches that breast cancer patients typically possess activate NF-kB. Thus, knowing that activated NF-kB reduces the chances of apoptosis and enhances metastasis, one would be motivated to administer DHMEQ to a breast cancer patient to inhibit further NF-kB activity, thereby reducing the symptoms of that cancer by reducing the chances of metastasis. Therefore, a method of administering DHMEQ to a patient with breast cancer is *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in absence of evidence to the contrary.

21. **Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Matsumoto et al. (Bio. and Med. Chem. Letters 10, 2000, 865-869) in view of Takeuchi et al. (US6566394; of record, see IDS) and Heymsfield et al. (Cancer, 1985, 55, 238-249), evidenced by Baldwin (J. Clinical Investigation, 2001, 107(3), 241-246) and Morishita et al. (US 6262033).**

22. Matsumoto and Takeuchi are relied upon for disclosure described in the rejection of claims 1 and 8 under 35 U.S.C. 103(a).

23. Matsumoto and Takeuchi fail to teach the symptom to be improved as weight loss.

24. The teaching of Heymsfield cures this deficiency. Heymsfield teaches that a loss in body fat accounts for a major portion of weight loss in cancer patients (see page 238, right column, 1st paragraph).

25. Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Matsumoto with Takeuchi and Heymsfield with a reasonable expectation for success in arriving at a method which improves the body weight of a cancer patient by administering DHMEQ. Matsumoto and Takeuchi are discussed above. Briefly, Matsumoto and Takeuchi motivate a method of administering DHMEQ to a patient with a tumor to reduce the symptoms of that tumor, especially leukemia. However, they fail to teach improving the body weight of a patient by such a treatment. Heymsfield specifically teaches that cancer patients lose body weight because of the cancer they are afflicted with. Therefore, it would be reasonable to assume that by treating cancer with DHMEQ, a patient would necessarily gain weight back as the cancerous cells are killed. It appears that Applicant is simply describing a direct result of the cancer treatment. Therefore, the invention as a whole is *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in absence of evidence to the contrary.

Conclusion

26. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kyle A. Purdy whose telephone number is 571-270-3504. The examiner can normally be reached from 9AM to 5PM.

27. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sharmila Landau, can be reached on 571-272-0614. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

28. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Kyle Purdy/
Examiner, Art Unit 1611
August 22, 2008

/Sharmila Gollamudi Landau/

Supervisory Patent Examiner, Art Unit 1611